Congenital Diarrheal Disorders in Neonates: A Single-Center Experience

Congenital diarrheal disorders (CDDs) are a group of inherited diarrheas with typical onset in the early neonatal period [1,2], with most being gene specific [3]. There is limited literature on the clinical spectrum and outcome of CDDs from India. Molecular genetic analysis has become the preferred diagnostic modality in recent years [4,5]. Here we report a case series of six cases of neonatal-onset chronic diarrhea (>14 days) with their outcomes over a 3-year period (2017- 2020) (**Table I**) [6].

Cases No. 1, 3 and 4: These patients were diagnosed with congenital glucose-galactose malabsorption (CGGM). All three developed diarrhea on exclusive breast feeds during the first week of life. Case No. 1 presented with osmotic diarrhea, hypoglycemia, hypernatremia and metabolic acidosis and septicemia. There was no evidence of immune deficiency. There was no improvement on hypoallergenic formula and total parenteral nutrition (TPN). The child eventually succumbed to fungal sepsis without a diagnosis. Next generation sequencing (NGS) sent 3 weeks prior to death provided the diagnosis of CGGM posthumously. Parents were advised prenatal counseling for the next pregnancy. Case No. 3 and 4 with CGGM had a very similar presentation. Oral rehydration solution (ORS) glucose challenge [8] was positive in both the cases. Endoscopic biopsy and electron microscopy were unremarkable. In view of history of consanguinity, lack of response to amino acid-based formula (AAF) and a clinical picture that resembled CGGM, they were commenced empirically on fructose-based special formula (FBF) pending the final reports of NGS (Next generation sequencing). There was dramatic clinical recovery with complete resolution of diarrhea within 48 hours and TPN was discontinued. Optimal and consistent weight gain was achieved prior to discharge. Molecular genetic analysis by NGS confirmed the diagnosis during follow-up. Both children, when last assessed at 2 years of age, were found to be thriving well and had achieved age-appropriate developmental and social milestones.

Case No. 2 and 5: These two patients were diagnosed with diacylglycerol acyltransferase (DGAT-1) deficiency. They presented during the second week of life with feed refusal and failure to thrive on exclusive breastfeeds. Formula feed supplementation also resulted in vomiting, dehydrating diarrhea and hypoalbuminemia. Continuous nasogastric infusion of AAF did not resolve the symptoms. Investigations did not reveal any evidence of sepsis or immune deficiency. Oral glucose challenge was negative. Endoscopic biopsies appeared to show nonspecific patchy villous atrophy with no viral inclusion bodies. Electron microscopy was normal. They were started on TPN while awaiting a genetic diagnosis. NGS confirmed DGAT-1 deficiency and they were treated with a special custom-made fat free infant formula, fat soluble vitamins and MCT oil. These children, in addition to dehydrating diarrhea and FTT, had recurrent vomiting, hypoalbuminemia, hypertriglyceridemia and occasional bulky/greasy stool classical of DGAT -1 deficiency. Case No. 2 is currently aged 18 months and has motor developmental delay. The child continues to fail to thrive on the fat-free specially formulated diet. Case No. 5 also responded to fat-free diet and showed slow weight gain, but is now lost to follow-up.

Case 6: This patient presented with neonatal cholestatic jaundice, osmotic diarrhea on exclusive breastfeeds and failure to thrive. The jaundice disappeared gradually but diarrhea and failure to thrive persisted despite adequate breastfeeds. The child continued to remain symptomatic even on supplemental

Table I Characteristics of Infants With Congenital Diarrheal Disorders

Case No.	*I*	*II*	*III*	*IV*	*V*	*VI*
Age (wk)	6	3	4	3	6	3
Age of onset (wk)	1st	2nd	1st	1st	1st	1st
Gender	F	M	F	F	M	M
Consanguinity	2nd degree	3rd degree	2nd degree	3rd degree	2nd degree	3rd degree
Birth weight (kg)	3.12	3.00	3.00	3.25	3.70	2.90
Weight at admission (kg)	2.37	1.99	2.22	2.10	3.78	2.60
Discharge weight (kg)	NA	3.34	2.65	2.99	3.98	3.57
TPN/PPN (d)	48	68	10	22	20	7
Hospital stay (d)	122	104	21	42	45	14
Diagnosis	Glucose galactose malabsorption	DGAT1 deficiency-fat malabsorption	Glucose galactose malabsorption	Glucose galactose malabsorption	DGAT1 deficiency-fat malabsorption	Congenital lactase deficiency
Treatment	Carbohydrate free, fructose-based formula	Fat free, protein rich formula	Carbohydrate free, fructose-based formula	Carbohydrate free, fructose-based formula	Fat free, protein rich formula	Hypoallergenic formula rich in MCT

All children survived except the first case.

infant formula. Serum total IgE levels were elevated, suggesting atopy. The child improved dramatically on a trial of hypoallergenic formula rich in MCT. NGS revealed an eventual diagnosis of congenital lactase deficiency. The baby is growing well and is now able to tolerate lactose-free cow milk protein containing infant formula at 9 months of age.

We, herein, describe the clinical spectrum of genetically confirmed CDDs; though electron microscopy aided diagnosis of MVID has previously been reported [9]. Our case series showed that congenital brush border enzyme deficiencies are the most common form of CDDs rather than congenital enteropathies or ion channelopathies. CGGM has autosomal recessive inheritance with classical triad of hypernatremia, hypoglycemia and metabolic acidosis [4,7]. All children with CDDs were born of consanguinity and diarrheal onset was within the first 2 weeks with classical triad. For DGAT-1 deficiency, literature cites resolution of diarrhea with fat free formula and a possible need for fat soluble vitamin supplementation and intra lipid infusions [10]. Both the neonates in our case series had resolution of diarrhea; however, had slow weight gain on fat free formula.

NGS has revolutionized the diagnostic approach to CDDs; however, it is expensive and turnaround time is late (4 weeks). It is more precise and is reliable than stool microscopy and stool electrolytes. The triad of clinical presentation, tissue electron microscopy and NGS form the cornerstone for apt diagnosis of CDDs. The management is individualized based on the molecular and tissue diagnosis and ranges from simple change to specialized specific diet to complex lifelong TPN.

Contributions: SSS,VHK: responsible for patient management, data collection and manuscript writing; NCK,SS: responsible for drafting the paper; NCK will act as guarantor of the study; CSS: helped in manuscript writing. The final manuscript was approved by all authors. *Funding*: None; *Competing interest*: None stated.

SHYAM SUNDAR SHARMA,[1] SRINIVAS SANKARANARAYANAN,[2] VAANATHI HEMENTHA KUMAR,[1*] NATARAJAN CHANDRA KUMAR,[1] C SHANMUGA SUNDARAM[1]

From [1]Departments of Neonatology and [2]Pediatric Gastroenterology,
Kanchi Kamakoti CHILDS Trust Hospital, Chennai.
**vaanathihementh@gmail.com*

REFERENCES

1. Guarino A, Spagnuolo M.I, Russo S, et al. Etiology and risk factors of severe and protracted diarrhea. J Pediatr Gastroenterol Nutr. 1995;20:173-78.
2. Berni CR, Terrin, G, Cardillo G, et al. Congenital diarrheal disorders: Improved understanding of gene defects is leading to advances in intestinal physiology and clinical management. J Pediatr Gastroenterol Nutr. 2010;50:360-66.
3. Ruemmele F.M. Chronic enteropathy: Molecular basis. Nestle Nutr Workshop Ser Pediatr Program. 2007;59:73-85.
4. Terrin G, Tomaiuolo R, Passariello A, et al. Congenital diarrheal disorders: An updated diagnostic approach. Int J Mol Sci. 2012;13:4168 85.
5. Thiagarajah JR, Kamin DS, Acra S, et al. Advances in evaluation of chronic diarrhea in infants. Gastroenterology. 2018;154:2045.
6. Younis M, Rastogi R, Chugh A, et al. Congenital diarrheal diseases. Clin Perinatol. 2020;47:301-21.
7. Anderson S, Koniaris S, Xin B, et al. Congenital glucose–galactose malabsorption: A case report. J Pediatr Health Care. 2017;31:506 510.
8. Lee WS, Tay CG, Nazrul N, et al. A case of neonatal diarrhoea caused by congenital glucose-galactose malabsorption. Med J Malaysia. 2009; 64:83-5.
9. Lingaldinna S, Sundaram M, Kamalarathnam CN, et al. Congenital fatal diarrhea in newborns. Indian J Pediatr. 2017;84:953-54.
10. Van Rijn JM, Ardy RC, Kuloðlu Z, et al. Intestinal failure and aberrant lipid metabolism in patients with DGAT1 deficiency. Gastroenterology. 2018;155:130-43.